cdisc

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Heterogeneity in RWD data sources: how to deal with it ?

Presented by Thierry Escudier and Manuel Neukum
EvidentIQ

Meet the Speakers

Thierry ESCUDIER

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Organization: EvidentIQ

Thierry Escudier is a senior leader in Clinical Operations with a high focus interest in digital innovation and patient centricity.

Manuel NEUKUM

Title: COO

Organization: EvidentIQ

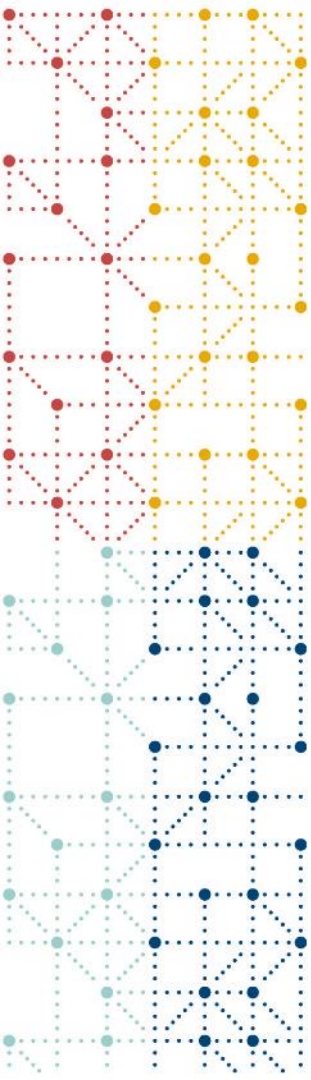
Manuel Neukum is the Managing Director of the software vendor XClinical and the COO of the EvidentIQ Group. He has been working in the clinical trial sector for over ten years and combines his industry and Software Engineering experience with his Data Science background.

Disclaimer and Disclosures

- *The views and opinions expressed in this presentation are those of the author(s) and do not necessarily reflect the official policy or position of CDISC.*

Agenda

1. RWD/RWE types and sources
2. Regulatory perspectives on heterogeneity of sources
3. How to manage heterogeneity ?



RWD and RWE

Heterogeneity of sources = richness of information

RWD and RWE: FDA definitions

Real World Data:

Real-World Data (RWD) are the data relating to patient health status and/or the delivery of health care routinely collected from a variety of sources.

Real World Evidence:

Real-world evidence is the clinical evidence regarding the usage and potential benefits or risks of a medical product derived from analysis of RWD.

Main difference between Randomised Clinical Trials and RWD studies

RCT studies:

- Protocol Design
- Homogeneous study population
- Limited to drug under evaluation
- Investigator driven
- Far from real life

RWD studies:

- Real World Setting
- Heterogeneous study population
- Various treatment option
- Healthcare Physician driven
- Close to real life

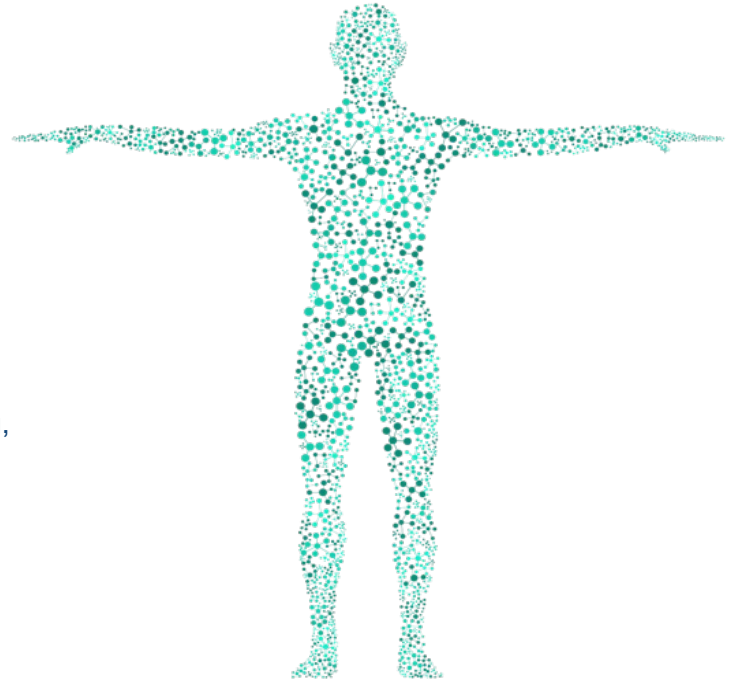
RWD have multiple profile types

CLINICAL
EHR, Lab test, Images

MEDICATION
Prescription, point of sale data, administration

CLAIMS
Medical, prescription drug, treatment use

MOLECULAR PROFILING
Genomic & Genetic data



PATIENT REPORTED
PROs, surveys, diaries

MOBILE HEALTH
Fitness trackers, wearables, Health apps

SOCIAL MEDIA
Patient communities, Facebook, Twitter

ENVIRONMENTAL
Climate, Pollutants, Lifestyle factors

FAMILY HISTORY
Extended family conditions & allergies

LITERATURE
Epidemiology, resource use, QoL measures

RWD are collected from different sources

Data produced by physicians:

- Patient registries and cohorts
- Medication orders
- Medical reports

Data generated during routine patient care:

- Databases (medical, administrative, etc.)
- Electronic health records

Data produced by patients:

- Online studies with self-reported data from patients
- Internet of Things (connected object/ medical device/ wearable device)
- Social networks
- Mobile apps

RWD and RWE are playing an increasing role in health care decisions

- Growing recognition that **real-life outcomes may differ from clinical trial** results
- A growing number of **innovative medicines entering the market at earlier** stages, triggering the need to better understand real-life use of these drugs
- Willingness to focus on patient needs and better involve patients in their care pathway
- Need to inform on product differentiation and to better evaluate treatments when an increasing number of options are available
- New ways to collect and analyze data in a real-life setting

The use of Real-World Evidence

The diversity of RWD/RWE enhance patient centricity

- Information on patient journey, unmet needs, quality of care, quality of life…
- Value of treatments/solutions from the patient perspective
- Monitoring real-world use of medicines.

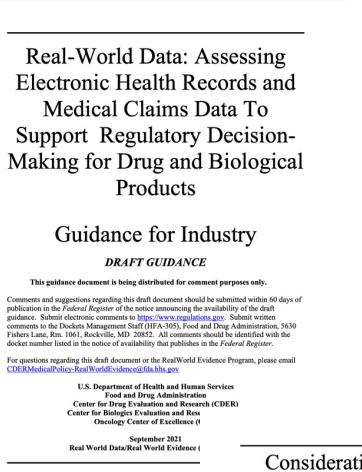
Regulatory perspectives: use of RWD/RWE for regulatory submission

Heterogeneity of sources = how to deal with it

Regulators encourage pharma to submit RWD/RWE for regulatory review

Key take away messages:

- In the past, HTA were the main users of RWD
- Now, regulators wish to access broader sets of data to enable them to support their regulatory decisions including approval of new indications for already approved drugs.



Real-World Data: Assessing Electronic Health Records and Medical Claims Data To Support Regulatory Decision-Making for Drug and Biological Products

Guidance for Industry

DRAFT GUIDANCE

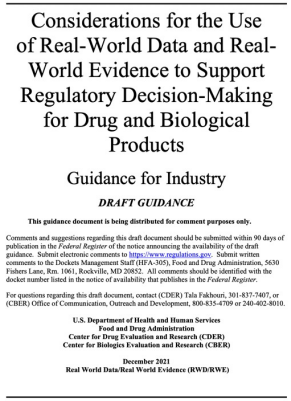
This guidance document is being distributed for comment purposes only.

Comments and suggestions regarding this draft document should be submitted within 60 days of publication in the *Federal Register* of the notice announcing the availability of the draft guidance. Submit electronic comments to https://www.regulations.gov. Submit written comments to the Dockets Management Staff (HFA-305), Food and Drug Administration, 5630 Fishers Lane, Rm. 1061, Rockville, MD 20852. All comments should be identified with the docket number listed in the notice of availability that publishes in the *Federal Register*.

For questions regarding this draft document or the RealWorld Evidence Program, please email CDERMedicalPolicy-RealWorldEvidence@fda.hhs.gov

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Res
Oncology Center of Excellence (

September 2021
Real World Data/Real World Evidence (



Considerations for the Use of Real-World Data and Real-World Evidence to Support Regulatory Decision-Making for Drug and Biological Products

Guidance for Industry

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For questions regarding this draft document, contact (CDER) Tala Fakhouri, 301-837-7407, or (CBER) Office of Communication, Outreach and Development, 800-835-4709 or 240-402-8010.

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research (CDER)
Center for Biologics Evaluation and Research (CBER)

December 2021
Real World Data/Real World Evidence (RWD/RWE)

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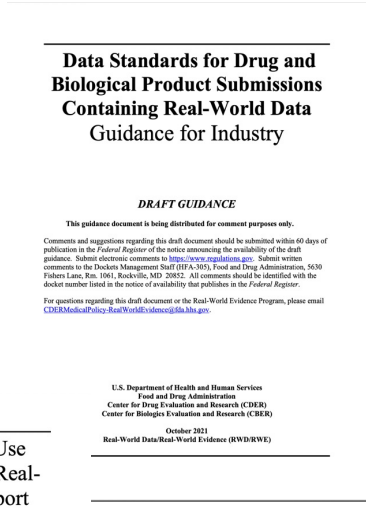
12/07/2021



Data Standards for Drug and Biological Product Submissions Containing Real-World Data
Guidance for Industry

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U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research (CDER)
Center for Biologics Evaluation and Research (CBER)

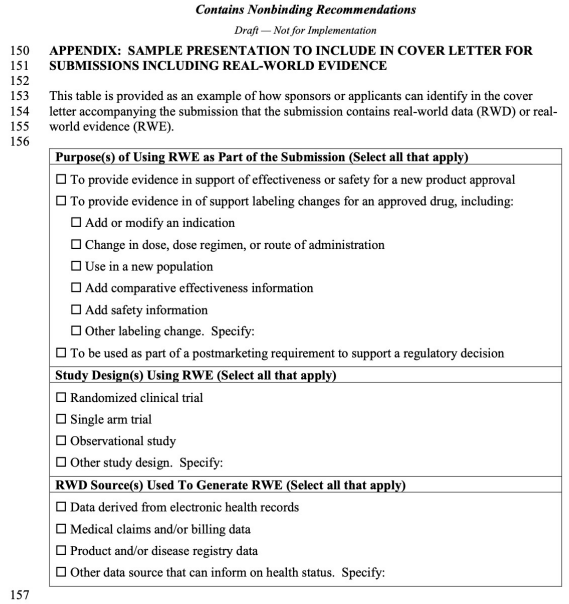
October 2021
Real-World Data/Real-World Evidence (RWD/RWE)

https://www.fda.gov/drugs/news-events-human-drugs/fda-issues-draft-guidances-real-world-evidence-prepares-publish-more-future

Regulators wish to address heterogeneity issue

Key Take away messages from all guidances:

- Make sure to evaluate impact of various data sources on overall data quality
- Explain the purpose of using RWD
- Prepare the list of all data sources of RWD to be submitted to FDA
- Make sure to be able to explain your data selection strategy if you have to make some selective choice *(observational studies)*
- Communicate upfront with FDA



Contains Nonbinding Recommendations

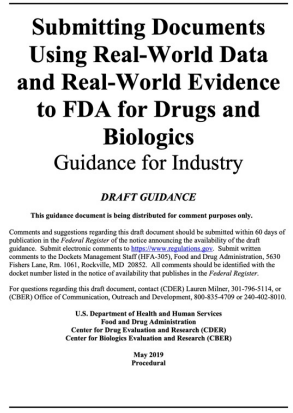
Draft — Not for Implementation

APPENDIX: SAMPLE PRESENTATION TO INCLUDE IN COVER LETTER FOR SUBMISSIONS INCLUDING REAL-WORLD EVIDENCE

This table is provided as an example of how sponsors or applicants can identify in the cover letter accompanying the submission that the submission contains real-world data (RWD) or real-world evidence (RWE).

Purpose(s) of Using RWE as Part of the Submission (Select all that apply)
☐ To provide evidence in support of effectiveness or safety for a new product approval
☐ To provide evidence in of support labeling changes for an approved drug, including:
☐ Add or modify an indication
☐ Change in dose, dose regimen, or route of administration
☐ Use in a new population
☐ Add comparative effectiveness information
☐ Add safety information
☐ Other labeling change. Specify:
☐ To be used as part of a postmarketing requirement to support a regulatory decision
Study Design(s) Using RWE (Select all that apply)
☐ Randomized clinical trial
☐ Single arm trial
☐ Observational study
☐ Other study design. Specify:
RWD Source(s) Used To Generate RWE (Select all that apply)
☐ Data derived from electronic health records
☐ Medical claims and/or billing data
☐ Product and/or disease registry data
☐ Other data source that can inform on health status. Specify:

5



Submitting Documents Using Real-World Data and Real-World Evidence to FDA for Drugs and Biologics

Guidance for Industry

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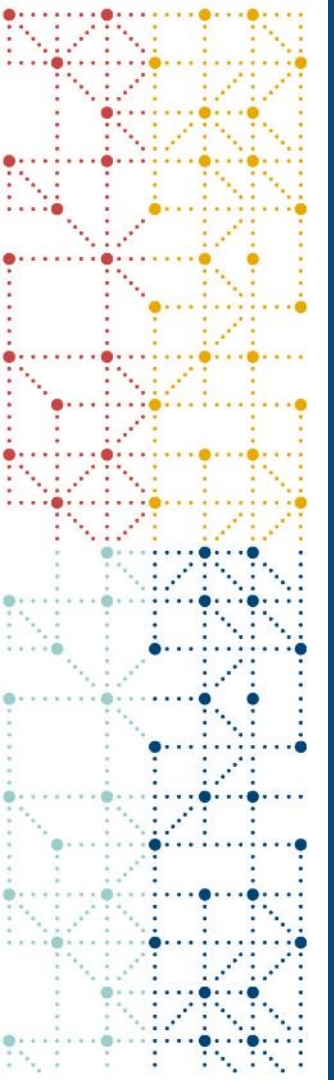
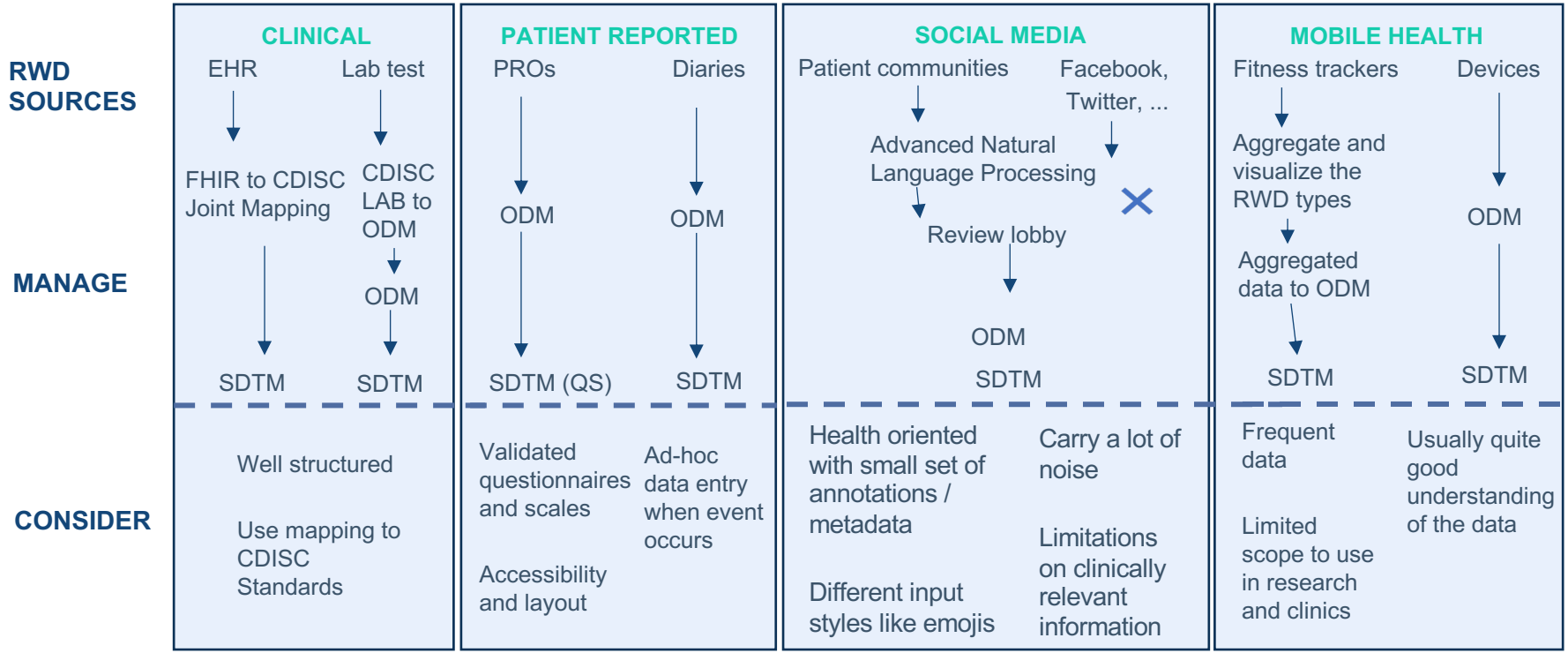
U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research (CDER)
Center for Biologics Evaluation and Research (CBER)

May 2019
Procedural



Examples on how to manage heterogeneity

How to manage data heterogeneity



Laboratory sample results

Mapping example of CDISC LAB to CDISC ODM:

Site Mapping

Subject Mapping

…

Single Result

```
<xsl:for-each select="//BaseTest">
  <xsl:value-of select="ancestor::Site[1]/@ID"/>
  <xsl:value-of select="ancestor::Visit[1]/../SubjectID"/>
  …
    <xsl:value-of select="../../SpecimenMaterial/@ID" />
    …
    <xsl:for-each select=".//SingleResult/child::*/@*">
    …
    </xsl:for-each>
  …
```

```
<ClinicalData StudyOID="R1398_2.0">
  <SubjectData SubjectKey="R1398_2.0-1">
  <SiteRef LocationOID="Center.003"/>
  <StudyEventData StudyEventOID="e_visit1">
    <FormData FormOID="f_lb" FormRepeatKey="001">
      <ItemGroupData ItemGroupOID="g_lbthromb">>
      <ItemData ItemOID="i_lbparam" Value="115"/>
      …
      <ItemData ItemOID="i_lborvalc" Value="464"/>
      …
      </ItemGroupData>
      …
```

ePROs/eDiaries

Use of pre-validated questionnaire libraries with mapping instructions to SDTM QS Domain:

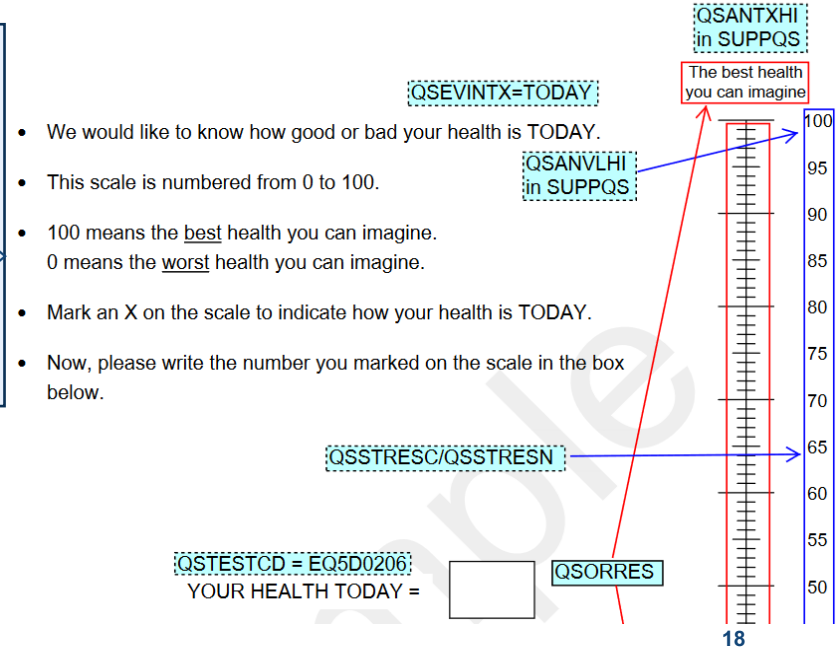
```
<ItemDef OID="i_scale" Name= "VAS" DataType="integer"
Length="3">
  <Question>
    <TranslatedText xml:lang="en">Vertical
Slider</TranslatedText>
   </Question>
   <xc:Config Key="display.style">slider.vertical</xc:Config>
   <xc:Config Key="min">1</xc:Config>
   <xc:Config Key="max">100</xc:Config>
   <xc:Config Key="theme">mono</xc:Config>
</ItemDef>
```

QSTESTCD = "EQ5D0206" QSTEST = "EQ5D02-EQ VAS Score"

QSORRES	QSSTRESC	QSSTRESN
The worst health you can imagine	0	0
The best health you can imagine	100	100

SUPPQS

QNAM	QLABEL	QVAL
QSANTXLO	Anchor Text Low	THE WORST HEALTH YOU CAN IMAGINE
QSANTXHI	Anchor Text High	THE BEST HEALTH YOU CAN IMAGINE
QSANVLLO	Anchor Value Low	0
QSANVLHI	Anchor Value High	100



Source: CDISC Website https://www.cdisc.org/standards/foundational/qrs

Patient Communities

Combine NLP models with annotations and comments of the forum:

- **Forum**: Symptoms and complications of type 2 diabetes
- **Conversation**: Sport and diabetes
- **Age**: 61
- **Gender**: female
- **Country**: UK

"Hello. I get very tired more and more often, I took up a bit more cycling recently but it was very hard and the slightest small hill was becoming very difficult
How to exercise in this case?
I don't know what to do, I talked to my doctor about it but he didn't have much to say... Thank you for your advice"

Patient Communities

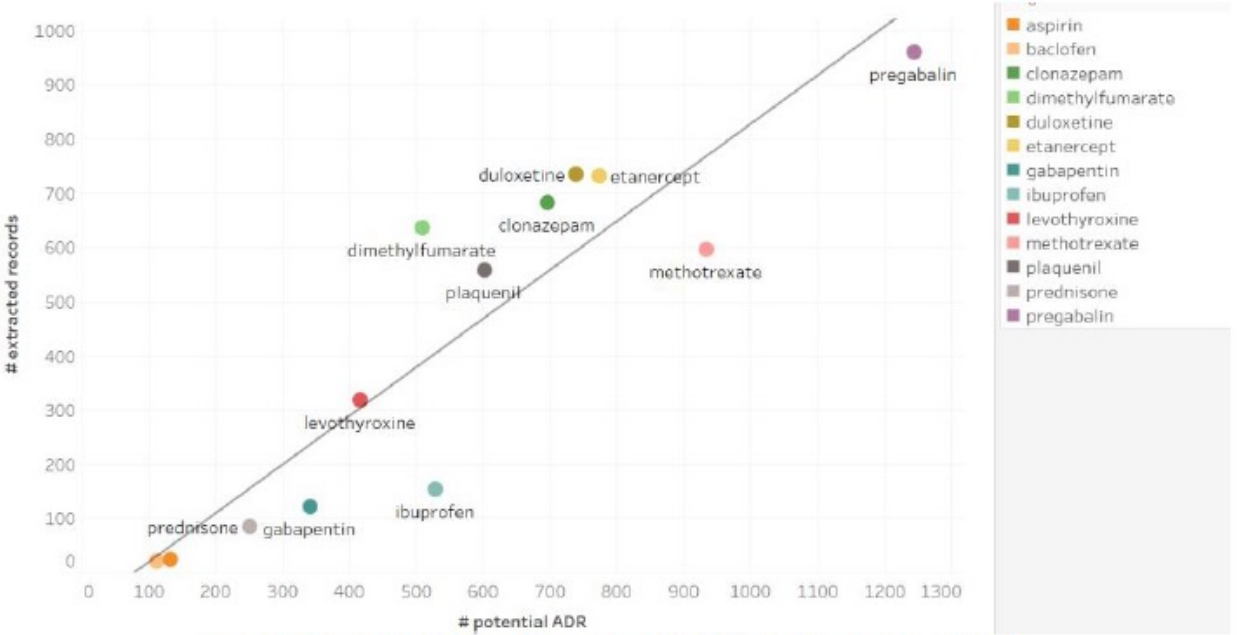


Figure 5: Potential ADR ratio on Carenity® (detection ratio = 108%)

Source: Publication Carenity/Keyrus 2019

Results on NLP models like Kusuri1 to:

- extract potential ADRs
- forward to Lobby for review
- create AEs in EDC or PV system

Thank You!